REMARKS

Entry of the foregoing amendments, reconsideration and re-examination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow are respectfully requested. By the present amendments, the specification has been amended to cure informalities. Additionally, prior claims 1-99 have been cancelled in favor of new claims 100-146. All of the new claims correspond to the elected methods for identifying compounds that modulate the T1R2/T1R3 sweet receptor.

Specific support for the recited assay methods can be found at pages 43-54 of the specification and especially the section entitled "Cell-based binding assays". Assay methods that monitor the effect of a putative sweet taste modulator on the effect of a known sweet ligand finds support at page 18 et seq.

The specification additionally has been amended to include the U.S. Serial number for the applications incompletely cross-referenced when this application was originally filed. As discussed with the Examiner, the "280606" recitation to the application filed on April 19, 2001 is application's client matter number for this application, not the serial number. Further, the serial number for the provisional application referred to by title, filed on June 26, 2001 has been added. This serial number was not yet assigned when this application was filed.

Turning now to the Office Action, applicants acknowledge the finality of the Restriction Requirement. Applicants respectfully advise that all of the current claims are directed to the elected assay methods.

The objection to the oath is noted. A substitute oath will be provided shortly. Applicants respectfully request that this objection be held in abeyance pending the receipt thereof.

The objection to the specification referral to "60/280,606" is noted. This objection is overcome by the insertion of the correct serial number which corresponds to the referenced case filed April 19, 2001, having this client matter number (not serial number).

The objection to the specification at page 69 is overcome by this amendment which amends this page to delete the underlining at line 12 and to insert the omitted alpha subscripts for G alpha 15.

The objections to the claims are moot as the prior claims are rewritten as new claims 100-146 which do not contain these informalities.

The potential for a double patenting rejection is noted. The examiner is respectfully advised that should such rejections be made, Applicants expressly reserve the right to traverse these rejections or to amend the claims in the conflicting case to overcome the rejection, if necessary.

Claims 3, 4, 9 and 10 are rejected as being broader than the enabling disclosure. Essentially the Examiner indicates that the specification only enables the production of functional hetero-oligomeric sweet taste receptors comprising two different T1R polypeptides if the cell used for expression thereof expresses a promiscuous G protein.

It is believed that this rejection is moot in view of the present amendments. In this regard, the current claims that refer to a G protein further require that the particular G protein be one that couples to the two expressed T1R polypeptides (T1R2 and T1R3) and results in a functional sweet taste receptor (receptor that responds to different naturally occurring and synthetic sweet compounds).

In this regard while promiscuous G proteins such as $G_{\alpha 15}$ and $G_{\alpha 16}$ are preferred, it is reasonable to assume that other G proteins, when expressed in a cell that co-expresses T1R2 and T1R3 will also result in a functional sweet taste receptor. Moreover, Applicants respectfully advise other G proteins are known and available. In fact the subject application cross references at page 10 various chimeric G proteins developed by the present Assignee which potentially can be substituted for $G_{\alpha 15}$. Contrary to the rejection, the selection of appropriate G proteins (i.e., those that couple with T1R2 and T1R3 to produce a functional T1R2/T1R3 sweet receptor) would not rise to the level of undue experimentation.

Finally, the Examiner's concern with respect to the recitation of the co-expression of "any gene" involved in gene signaling is moot. The current claims do not contain this verbiage.

Based on the foregoing, withdrawal of the §112 first paragraph rejection is earnestly solicited.

Claims 1-11 stand rejected under 35 U.S.C. §112 first paragraph as being indefinite. This rejection is respectfully traversed to the extent it may be applicable to the current claims.

First, the Office Action indicates that measuring receptor "activity" is indefinite. The Office Action suggests that "measuring an intracellular signaling activity" should be substituted therefor. The position of the Examiner is respectfully traversed.

The present claims are directed to assays for identifying compounds that modulate, inhibit or enhance the activity of a hetero-oligomeric sweet receptor produced by co-expression of T1R2 and T1R3 polypeptides in a host cell, by detecting the effect of said compound on the activity of said receptor. It would be well understood to a skilled artisan in possession of the subject specification and claims, which are directed to cell based assays, that these cell-based activity assays could be effected by different, well-known methods for detecting the activity of a GPCR.

Therefore, it would be readily comprehended to the skilled artisan what is intended to fall within the scope of the present claims. This especially would be clear upon review of the section of this application at pages 50-53 which articulates a number of conventional techniques used to measure the effect of target compounds on the activity of a particular G protein coupled receptor. In order to make this abundantly clear Applicants have added a number of claims directed to different means of assaying the activity of the subject sweet taste receptor. To require Applicants to limit their claims to a particular method for evaluating receptor activity is therefore not necessary for an understanding of the invention and indeed would unjustifiably compromise the scope of Applicants' invention.

The suggestion for an end step in independent claim 1 (new corresponding to claims 100 and 101) has been essentially adopted herein. The new claims provide for the detectable change in receptor activity to correlate to the putative sweet taste modulator being identified as a sweet taste modulator, inhibitor or enhancer.

The objection to prior claims 6 and 7 is moot as the current claims do not suffer from noted antecedent basis criticisms.

Based on the foregoing, withdrawal of the §112 second paragraph rejection is respectfully requested as the current claims are definite and particularly define what Applicants regard to be their invention.

Claims 1-11 stand rejected under 35 U.S.C. §103(as) as allegedly being rendered obvious by Zuker et al., U.S. Patent 6,383,778 in view of Montmayeur et al. This rejection is respectfully traversed.

However, prior to specifically addressing the rejection, the novel and non-obvious features of the present invention are summarized. It is believed that this should facilitate a better understanding of the invention and why the invention is not fairly suggested by the cited references.

Essentially the present invention involves the discovery that cells can be obtained which co-express T1R2 and T1R3 to yield a functional sweet taste receptor, referred to herein as T1R2/T1R3 that responds to different sweet taste stimuli. As evidenced by the data referenced in the experimental examples (*See e.g.,* Figure 4 and Figure 5) HEK-G15 cells which co-expressed T1R2 and T1R3, when assayed by imaging, and which were incubated with different fluorescence taste stimuli including sucrose, tryptophan, neonate, cyclamate, asceulfane and aspartame, exhibited detectable differences in receptor activity. By contrast, cells which only expressed T1R2 or T1R3 did not exhibit a response to any of these sweet compounds when assayed by the same methods. Therefore, the present application contains a convincing demonstration that cells which co-express T1R2 and T1R3 express a functional sweet taste receptor, and that the activity of this receptor can be measured in the presence of specific compounds that modulate the sweet receptor. This is

demonstrated by the fact that seven different sweet compounds were shown to activate this receptor. (*See* Figures 4 and 5 of this application).

Thus, the application provides an actual reduction to practice of the claimed cell-based assay methods for detecting whether a particular compound is a sweet taste modulator based on its effect on the activity of the T1R2/T1R3 receptor in cells which co-express these proteins. This is a highly significant advance in the art as these methods have broad application in the identification of novel sweet molecules as well as the identification of compound which modulates, e.g., enhances or inhibits sweet taste elicited by known sweet molecules such as sucrose, saccharin and aspartame. Such modulators have substantial potential, e.g., they may reduce the required concentrations of other known natural or synthetic sweet compounds necessary to obtain a composition having a desired sweetness. Thereby, lower-calorie compositions may be obtained which still posses a desired sweet taste. Also, such modulators may reduce or eliminate undesired effects of some synthetic sweeteners, e.g., the bitter taste associated with saccharin. Applicants respectfully submit that the claimed assay methods and associated advantages are not fairly suggested by the cited references.

The cited Zuker patent certainly does not teach or suggest the claimed invention. Rather, the patent only teaches that mammals express GPCR genes referred o therein as GPCR-B3 (T1R1) and GPCR-B4 (T1R2) that are involved in taste perception. However, this patent does not teach the T1R3 gene, a requirement of all of the present claims. Also, this patent does not teach or suggest that the co-expression of T1R2 and T1R3 in a suitable host cell would yield a hetero-oligomeric sweet taste receptor that responds to both naturally occurring and synthetic sweet taste stimuli. Nor does the Zuker patent teach or suggest that T1R2/T1R3 co-expressing cells would be useful in cell-based assays for identifying compounds that modulate the sweet taste receptor. Thus, Zuker, at least taken singularly, does not suggest the present invention.

Zuker is however combined with Montmayeur et al. At the outset, Applicants note that they reserve the right to antedate this reference which was published in May

of 2001, less than 2 months prior to the following date of this application. However, Applicants believe that their should not be necessary as this reference does not render the present invention obvious.

The Montmayeur publication relates to the identification of the T1R3 gene. As properly noted by the Examiner, the reference teaches that T1R3 is expressed in a subset of taste cells and that most of these cells also express T1R2. Also, the authors suggest that sequence differences in the T1R3 polypeptide in mice correlate to different Sac phenotypes (identified as "tasters" and "non-tasters").

However, this reference does not fairly suggest the claimed methods which use cells which co-express T1R2 and T1R3 as assay tools to identify sweet taste modulators. Rather, this reference merely contains an unsubstantiated allegation that T1R2 and T1R3 may be expressed as a heterodimer. There is no experimental evidence to support this supposition other than their observation that many, not all taste cells which express T1R3 also express T1R2. In fact, the authors are not even certain that T1R3 is a taste receptor, much less that T1R2/T1R3 expressed in combination is necessary to yield a functional sweet receptor.

The attention of the Examiner is respectfully directed to page 496, left hand column wherein Montmayeur et al., speculates several possibilities for T1R3 including that it may not even be a sweet taste receptor. Particularly, they suggest that T1R3 may be expressed as a heterodimer with T1R1 and T1R2, that the T1Rs may function separately, and that the receptor may exist as both homodimers and heterodimers. Also, on the right column of the same page, Montmayeur further indicates that prior mice studies suggest that there may be "more than one sweet receptor", and that "the actual number of receptors that detect sweet compounds remains to be determined".

Accordingly, in view of their results, they speculate that "if T1R3 is indeed a sweet receptor" that all three T1Rs may be sweet receptors or possibly that different T1R homodimers and heterodimers may have different ligand specificities.

Based on these disparate theoretical teachings in the reference, this reference does not reasonably suggest that the co-expression of T1R2 and T1R3 in host cells

would yield a functional taste receptor that specifically responds to sweet taste stimuli. At best, the rejection renders the invention obvious to try.

However, this is not the appropriate standard for obviousness under §103. Rather, an appropriate §103 rejection requires that the prior art alone or in combination render the claimed invention obvious to do with a reasonable expectation of success. Herein the cited references do not satisfy this test. Indeed, the cited reference concedes that they were uncertain whether T1R3 encodes a functional taste receptor, much less that co-expression of T1R2 and T1R3 is necessary to obtain a functional sweet taste receptor.

Thus, withdrawal of the §103 rejection based on the Zuker patent in view of Montmayeur et al., is respectfully requested.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding, the Examiner is respectfully requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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